REMARKS

Claims 16-18 and 24 are pending in the application. The amendment to claim 24 makes grammatical changes to more clearly point out the subject matter that Applicants regard as their invention, and corresponds to the Examiner's suggestion made in Paper No. 33. No new matter is added by way of the amendments.

Grounds of Claims Rejections/Objections Withdrawn under 35 USC § 103 (a)

Applicants are pleased to note the withdrawal of the claim rejections under 35 USC § 103 (a) regarding GenBank Accession No. MMU87814 (Lasky, submitted January 29, 1997) in view of Ackerman.

Grounds of Claim Rejections Maintained under 35 USC § 103 (a)

Claims 16-18 and 24 stand rejected under 35 USC § 103 (a) as allegedly being obvious over Database GenBank Accession No. AI322422 (Marra, et al, 1996) in view of Ackerman (*Human Cell* 1:46-53, 1988). Applicants respectfully submit that the rejection is overcome by the arguments set forth below.

The Examiner based his rejection upon a primary reference which the Examiner alleges :

> "...teaches the polynucleotide sequence of a messenger RNA molecule, which would be reasonably expected to encode a polypeptide. As a 507 nucleotide region of the polynucleotide sequence of the prior art is 99% similar to the polynucleotide sequence set forth in SEQ ID NO:2, it would be reasonable to expect that the amino acid sequence of the protein encoded by the polynucleotide sequence of the prior art would be very similar to the amino acid sequence set forth in SEQ ID NO:1, which is encoded by the polynucleotide sequence for SEQ ID NO:2."

Thus, because one of the three possible predicted amino acid sequences that could be read from the polynucleotide sequence of the cited reference is very similar to a portion of the amino acid sequence of PSTPIP, the Examiner argues that it is reasonable to expect that an antibody produced by immunizing an animal with the (appropriately selected) polypeptide encoded by the nucleic acid molecule of the prior art would bind the polypeptide of SEQ ID NO:1.

Applicants respectfully traverse the rejection for at least the reasons discussed below. In addition, in traversing the rejection, Applicants respectfully note that the Examiner acknowledges that Marra does not disclose the subject matter of claims 16-18 and 24: "However, Gen bank Accession No. AI322422 does not disclose antibodies that bind to the protein encoded by the nucleic acid molecule; nor does it disclose specifically disclose monoclonal antibodies, hybridomas that produce antibodies, or detectably labeled antibodies." (page 16, paragraph 4 of point 20, Paper No. 28).

To establish a *prima facie* case of obviousness, three basic criteria must be met.

> In order to establish a prima facie case of obviousness, there must be 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the Applicants' disclosure.

In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The nucleic acid fragment

Applicants claim antibodies to the full length functional polypeptide of SEQ ID NO:1. Applicants respectfully submit that Marra teaches a fragment nucleotide sequence without a reading frame. Thus, Marra provides a nucleotide sequence possibly encoding three different amino acid sequences that may or may not encode a functional protein. Further, Marra provides no teaching to determine the appropriate

reading frame to encode a portion of the polypeptide of SEQ ID NO:1. Marra provides no suggestion as to which, if any, of the three sequences might be expressed in nature. Marra not providing any motivation to choose one or another of the possible amino acid sequences, Applicants respectfully submit that it is only with the benefit of the Applicants' disclosure and with hindsight that one might argue that Marra suggests a portion of SEQ ID NO:1.

Applicants presented this argument in Applicants' Response mailed June 7, 2002. However, to date, Examiner has not responded to this argument. Applicants respectfully maintain that, without the benefit of Applicants' known polypeptide sequence, one skilled in the art would not have known the proper reading frame of the fragment nucleotide sequence to determine the appropriate fragment polypeptide sequence of Applicants' full length polypeptide.

The polypeptide fragment

Even if Marra had provided a reading frame, which it did not, the reference only provides for less than ½ of the Applicants' full length polypeptide. The nucleotide sequence of the prior art is a 507 base pair sequence that could, if one had the appropriate reading frame, encode only 169 amino acids of the 414 amino acids of Applicants' polypeptide of SEQ ID NO:1. Neither the primary reference nor the Examiner provide any teaching on how to obtain the rest of the polypeptide of SEQ ID NO:1.

Here, the prior art teaches a polynucleotide which, upon identification of the proper reading frame, is predicted to encode only 169 amino acids of the 414 amino acids of the polypeptide of SEQ ID NO:1. Significantly, the prior art predicted fragment lacks 245 amino acids on the N-terminus portion of the polypeptide of SEQ ID NO:1.

Applicants' specification discloses that this type of deletion in the polypeptide would disrupt and destroy the structural integrity and biological activity of the prior art

predicted amino acid fragment. "The results disclosed in the examples show that the N-terminus of PSTPIP is required for the formation of a correctly folded protein that is capable of binding PTPHSCF." (See Specification p 20, line 35 - 36) "Accordingly, if structural integrity and biological activity are to be retained, any N-terminal deletion should not extend beyond about 25 amino acids of the murine PSTPIP Sequence or the corresponding amino acids in the human or other mammalian sequences." (See specification page 20, line 35 - 39, page 41, line 1 - 8, and page 45, line 11 - 29.) The predicted protein of the primary reference contains not just a 25, 50 or 75 amino acid deletion in the N-terminus region as disclosed in the specification, but a 245 amino acid deletion in the N-terminus region of the polypeptide of SEQ ID NO:1. As demonstrated by the examples in the specification, this deletion in the reference protein would disrupt the structural integrity and biological activity of the protein.

"Close structural similarity alone is not sufficient to create a *prima facie* case of obviousness when the reference compounds lack utility, and thus there is no motivation to make related compounds." MPEP 2144.08 II A 4 (d) "In order to find such motivation or suggestion there should be a reasonable likelihood that the claimed invention would have the properties disclosed by the prior art teachings." MPEP 2144.08 II A

Without a properly folded, functional protein, one skilled in the art would not reasonably expect a "common epitope" between the prior art fragment and the polypeptide of SEQ ID NO:1. Without a common epitope on the polypeptide of the primary reference, one skilled in the art would not have a reasonable expectation of success nor would it have been obvious to one of skill in the art at the time of the invention to produce the claimed antibodies, monoclonal antibodies, hybridoma cell lines nor detectably labeled antibodies. Without impermissible hindsight, Applicants submit, the claims are not obvious.

The antibodies

The Examiner stated: "One would have been motivated to manufacture the antibody that binds the polypeptide encoded by the nucleic acid molecule of the prior art by immunizing an animal with a polypeptide comprising at least a portion of the predicted amino acid sequence encoded by the nucleic acid molecule, because the utility of such antibodies was much appreciated in the art at the time the invention was made." (page 6, paragraph 5 of point 7, Paper No. 33).

However, Applicants further respectfully submit that there is no suggestion or motivation in Marra or in the knowledge of one of skill in the art at the time of the invention to produce antibodies to the peptide fragment encoded by the proper reading frame of the nucleic acid molecule of Marra.

The Examiner has stated that Marra does not provide antibodies (*supra*). Instead, as quoted above, the Examiner has argued that, having selected the proper reading frame and produced an antibody fragment, one of skill in the art would then be motivated to produce antibodies to that fragment. Applicants respectfully disagree. Such an argument ignores the fact that, at the time of the invention: 1) there was no known full-length polypeptide corresponding to the fragment; 2) there was no known function for either the fragment or the (unknown) full-length polypeptide; and 3) there was no evidence that the fragment would assume a conformation similar to that of the corresponding portion of the full-length polypeptide (if the fragment conformation is different, antibodies raised against the fragment would not be expected to bind to the full-length polypeptide: "Proteins are so precisely built that the change of even a few atoms in one amino acid can sometimes disrupt the structure of the whole molecule so severely that all function is lost." Albert, B., et.al., (2002) *Molecular Biology of The Cell*, 4th edn. New York, Garland Science p. 142).

Accordingly, Applicants respectfully submit that at the time of the invention there was no motivation in the reference or in the art to produce the claimed antibodies.

It is only Applicants' teaching in the present application, providing a full-length polypeptide and a function for the same, that provides such a motivation. However, "The invention must be viewed not with the blueprint drawn by the inventor, but in the state of art that existed at the time." Interconnect Planning Corp. v. Feil, 227 USPQ 543, 547 ((1985). It is "...improper to use the patent as an instruction manual to lead to elements of prior art." Panduit Corp. v. Dennison Manufacturing Co., 810 F 2d 1561, 1568 (Fed Cir. 1987). "Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.' " E.g. Grain Processing Corp. v. American Maize-Products Corp., 5 USPQ2d 1788, 1792 (Fed. Cir. 1988).

Applicants respectfully submit that it would require impermissible hindsight to obtain the correct reading frame from the nucleotide fragment of Marra; to forecast the functionality of the fragment protein obtained; and to forecast a use for the antibodies raised to that protein.

Referring to an lower court decision, the United States Court of Appeals for the Federal Circuit stated in *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.* (806 F.2d 1565,1576) "the district court's analysis employed an inappropriate "would have been able to produce" test." Applicants respectfully submit that it is only by such an inappropriate "would have been able to produce" test that Marra might be seen as making obvious the antibodies of claims 16-18 and 24.

Moreover, in order to support a claim of obviousness, in addition to motivation, one must have had a reasonable expectation of success at the time of the invention. However, at the time of the invention one only had a fragment of the full-length protein, so one would not have had a reasonable expectation that such a fragment would fold appropriately to provide antibodies that would recognize epitopes on the full-length polypeptide. See, for example, the discussion *supra* under the heading "The

Polypeptide Fragment." Applicants note the Examiner's statement: "An antibody that binds a common epitope will bind both proteins" (page 5, paragraph 4 of point 7, Paper 33). However, Applicants respectfully note that a common epitope implies common three-dimensional structure, and that a fragment that is mis-folded compared to a full-length protein may not be recognized by an antibody to the full-length protein. More importantly to the Examiner's contention that an antibody raised against a polypeptide fragment encoded by the nucleic acid of Marra would be identical to the claimed antibodies, Applicants respectfully note that an antibody raised against a mis-folded polypeptide fragment would not necessarily be expected to recognize an epitope of the corresponding full-length protein.

Accordingly, one of skill in the art at the time the invention was made would not have had a reasonable expectation of success of providing antibodies capable of recognizing epitopes of the PST phosphatase interacting protein using the polypeptide fragments encoded by a selected reading frame of the nucleic acid of Marra.

Applicants respectfully submit that the Examiner has not met the initial burden of establishing a prima facie case of obviousness. Without impermissible hindsight, the cited references fail to provide the requisite motivation and fail to provide a reasonable expectation of success that one skilled in the art could modify the reference fragment EST to produce a functional properly folded, biologically active polypeptide against which one could reasonably expect to raise the claimed antibodies. Accordingly, the cited reference combined with the knowledge of one of ordinary skill in the art at the time of the invention fail to provide all the elements of the claimed inventions of claims 16-18 and 24; fail to provide suggestion of the proper reading frame to provide even a fragment of the PST interacting protein against which to raise antibodies; and fail to provide motivation to attempt to raise such antibodies; fail to provide a reasonable expectation of success that such antibodies would recognize the (then unknown and of unknown length) full-length protein.

In view of the foregoing arguments, Applicants submit that claims 16-18 and 24 are patentable over Marra in view of Ackerman. Applicants respectfully request withdrawal of the rejection of claims 16-18 and 24 under 35 USC § 103 (a).

New Grounds of Claim Rejections under 35 USC § 112 Paragraph 1

The Examiner rejected Claims 16-18 and 24 under 35 USC § 112, Paragraph 1 as containing subject matter which was not contained in the original specification. Specifically, the Examiner alleged an inadequate antecedent basis in the specification for the limiting amendment to claim 24 which states, "at a site not including phosphorylated tyrosine"

Examiner alleges this limitation creates a subgenus of antibodies not described by the original disclosure and further, that it presents a negative limitation which introduces new concepts.

Applicants claim antibodies which are capable of binding to the full length PSTPIP polypeptide. In studying the *in vivo* tyrosine phosphorylation of PSTPIP, Applicants identified two distinct antibodies, the anti-PSTPIP (α PSTIPI) and anti-phosphotyrosine (α Ptyr) antibodies. See specification page 4 line 34 and 35. "If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See *In re Johnson* 194 USPQ 187, 196 (CCPA 1977)." MPEP 2173.05 (i). In this case, Applicants have alternatively recited anti-phosphotyrosine antibodies and anti-PSTPIP antibodies which lack phosphorylation. Having alternatively recited these two antibodies in the specification, Applicants may expressly exclude one alternative from the claims.

Based upon the foregoing arguments, Applicants respectfully submit this rejection should be withdrawn.

New Grounds of Claim Rejections under 35 USC § 112 Paragraph 2

The Examiner rejected Claims 16-18 and 24 under 35 USC § 112, paragraph 2

as being indefinite because of the limiting phrase which recites, "within said SEQ ID NO:1". Examiner suggested amending the claim to eliminate this limitation. Hence, Applicants have eliminated the phrase and amended the claim to obviate the Examiner's rejection. Withdrawal of the rejection is respectfully requested.

CONCLUSION

For the reasons presented above, Applicants respectfully submit that all pending claims are in condition for allowance, and an early action to that effect is respectfully solicited.

If any issues remain or require further clarification, the Examiner is respectfully requested to call Applicants' counsel at the number listed below in order to resolve such issues promptly.

The Commissioner is authorized to charge the appropriate fees of $2,720.00 for the Request for Continued Examination and Request for Extension of Time of five months, as well as, any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing attorney's docket no. **39766-0061 CP2**.

Respectfully submitted,

Dated: June 26, 2003

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